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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/652,814	08/29/2003	Gretchen M. Unger	3193.01US03	2748

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EXAMINER	
POPA, ILEANA	
ART UNIT	**PAPER NUMBER**
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/652,814	UNGER, GRETCHEN M.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *66-95,97-109,111-116,118,119,122-124,126,127 and 133-136* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *66,67,87-94,101 and 133-136* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 68-86,95,97-100,102-109,111-116,118,119,122-124,126 and 127.

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

2. Claims 1-65, 96, 110, 117, 120, 121, 125, and 128-132 have been cancelled. Claims 68-86, 95, 97-100, 102-109, 111-116, 118, 119, 122-124, 126, and 127 have been withdrawn. Claims 66, 133, and 134 have been amended. Claims 135 and 136 are new.

Claims 66, 67, 87-94, 101, and 133-136 are under examination.

Response to Arguments

Double Patenting

3. Claims 66, 67, 87, 88, 90, 92-94, 101, 133, and 134 remain provisionally rejected and the new claim 136 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, and 8 of copending Application No. 10/378,044.

Claims 66, 87, 88, 90, 92-94, 101, 133, and 134 remain provisionally rejected and the new claim 136 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10 and 13 of copending Application No. 10/958,999.

Claims 66, 67, 87-94, 101, 133, and 134 remain rejected and the new claim 136 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 29 and 42 of U.S. Patent No. 6,632,671.

Applicant acknowledged the instant rejections, however, since a terminal disclaimer has not been provided, the rejections are maintained. The new claim 136 is included in the instant rejection because the above applications and patent teach the limitation of 2,4,7,9-tetramethyl-5-decyn-4,7-diol (see also the prior Office action).

The objection to claim 90 as being a substantial duplicate of claim 87 is withdrawn in response to Applicant's argument filed on 01/05/2007.

Claim Rejections - 35 USC § 102

4. Claims 66, 67, 87, 88, 90-92, 94, and 101 remain and the new claim 135 is rejected under 35 U.S.C. 102(e) as being anticipated by Unger, E.C. et al. (US Patent No. 6,139,819), for the reasons of record set forth in the prior Office action. Applicant's arguments filed on 01/05/2007 have been fully considered but they are not persuasive. Additionally, the Declaration under 37 CFR 1.132 filed 12/14/2006 is insufficient to overcome the instant rejection for the reasons shown below.

Applicant traversed the instant rejection on the grounds that:

(i) Unger et al. do not teach encapsulating a bioactive component and a surfactant and the use of the term encapsulation refers to gases or gaseous precursors (column 30, lines 18-32).

(ii) the claimed invention is directed to a narrow range of particle size, while Unger et al. teach a broad range and therefore, it is reasonable to conclude that Applicant's narrow range is not disclosed with sufficient specificity by Unger et al. Applicant argues that Unger et al. do not disclose methods to produce particles of about 50 nm, wherein the particles incorporate a bioactive agent, a surfactant having an HLB value of less than 6.0, and a biocompatible polymer for specific cellular uptake. Applicant submits that none of the examples in Unger et al. disclose a vesicle of less than 200 nm and even if various methods of preparing liposomes are disclosed by the specification, (column 61, lines 12-67), wherein some methods can yield liposomes of 30 or 60 nm in diameter (see U.S Patent No.4,921,706, incorporated by reference by Unger et al.) , these methods would not result in the particles of the instant invention because they would not have a bioactive component core, a surfactant, and polymers for specific cellular uptake, wherein the particles have a diameter of less than 50 nm. Applicant submits the use of Tween 80 or Tween 20, as disclosed by Unger et al. (column 34, line 3, Example 11), will not result in particles having a diameter of about 50 nm and that such particles can be obtained only by Applicant's novel methods of manufacture. For these reasons, the disclosure of Unger et al. with respect to the 50 nm particles is not enabling because achieving such particles based on the disclosure would require undue experimentation.

(iii) Unger et al. primarily teach vesicles, particularly liposomes (i.e., bilayers of lipid molecule), whereas Applicant's invention is directed towards particles wherein the surfactant forms a monolayer. Applicant argues that the art recognizes the term micelle

as refering to monolayer structures and the term vesicle as refering to bilayer structures. Since Unger et al. do not redefine the terms "monolayer", "bilayer", or "liposome" contrary to art-accepted definitions, the monolayer vesicles of Unger et al. (column 7, lines 28-59) must refer to a single bilayer structure, and one of skill in the art would understand that such vesicles would not include monolayer micelles.

(iv) the teaching of Unger et al. of a size of 30 nm is for vesicles only (i.e., bilayer structures) and therefore does not anticipate the instant invention because the instant invention teaches monolayer structures.

For the reasons above, Applicant requests the withdrawal of the rejection.

Applicant's arguments are acknowledged, however, the rejection is maintained for the following reasons:

(i) It is noted that the instant claims do not recite encapsulating a bioactive component and a surfactant, they recite a surfactant shell that surrounds the association between the bioactive component and the surfactant; surrounding does not equal encapsulation. However, it is noted that Unger et al. do teach that the biocompatible polymer forms a shell that surrounds the association between the bioactive component and the surfactant. Specifically, Unger et al. teach particles comprising a core provided by paramagnetic contrast agents, a surfactant molecule, such as cetyl alcohol, which is associated with a bioactive component, and a biocompatible polymer that coats the association between the bioactive component and the surfactant, wherein the biocompatible polymer provides specific cellular uptake; by

coating this association they could also prevent the loss of gases (i.e., they provide encapsulation of the gases or gas precursors) (column 14, lines 10-12, column 28, lines 37-47, column 30, lines 18-32). Therefore, it is the biocompatible polymer coating (i.e., surrounding) the association that provides encapsulation and prevents the loss of gases or gases precursors. It is noted that Unger et al. teach that their particles are used for the delivery of both contrast and bioactive agents, wherein the agents form the core of the particles and are associated with the surfactant molecules (column 9, lines 36-49, column 23, lines 38-43, columns 55 and 56, column 59 bridging column 60).

(ii) Unger et al. do not need to provide examples for preparing particles of each size to be enabling. In Remarks and in the Declaration, Applicant argues that the instant particles are only obtainable by Applicant's novel method of manufacture, while Unger et al. disclose only conventional methods. However, apart from reviewing the art and the examples provided by the specification, Applicant did not provide any evidence that conventional methods cannot be used to prepare particles that are similar to the claimed particles. Applicant just argues that even if some of the disclosed conventional methods yield liposomes of 30 or 60 nm in diameter (see U.S Patent No.4,921,706, incorporated by reference by Unger et al.), these methods would not result in the particles of the instant invention because they would not have a bioactive component core, a surfactant, and polymers for specific cellular uptake, wherein the particles have a diameter of less than 50 nm. Again, this is an argument not supported by any evidence. First, as stated above, Unger et al. do teach particles comprising a core provided by paramagnetic contrast agents and bioactive agents, a surfactant molecule,

such as cetyl alcohol, which is associated with a bioactive component, and a biocompatible polymer that forms a shell surrounding the association between the bioactive components and the surfactant, wherein the biocompatible polymer provides specific cellular uptake. Therefore, Unger et al. teach all the components that are claimed as forming the instant particles. Second, with respect to the particle size, the instant specification clearly discloses that the use of a surfactant with a HLB value about 5.0 units (such as cetyl alcohol) results in particles with a diameter of about 50 nm (p.5, paragraph 0063, claims 1 and 90). Since Unger et al. teach that cetyl alcohol can be used to prepare their particles, these particles must have a diameter of about 50 nm and. Therefore, absent evidence to the contrary, the particles of Unger et al. are not different from the instant particles. It is noted that Unger et al. do not teach that Tween 80 and 20 as surfactants associated with the core of bioactive components; Unger et al. teach that Tween 80 and 20 are just embodiments of auxiliary stabilizing materials and not of surfactants that are associated with the bioactive components (see column 33 lies 44-67, column 34, lines 1-3), wherein Tween 80 and 20 may or may not used as auxiliary components for the particles of Unger et al. Therefore, Applicant's argument that the use of Tween 80 and 20 will not result in particles having a diameter of about 50 nm is not persuasive. For the same reasons, the Declaration under 37 CFR 1.132 filed 12/14/2006 is insufficient to overcome the instant rejection.

(iii) and (iv) It is also noted that, contrary to Applicant's arguments, claims 66, 67, 87-94, 101, 133, 134, and 136 are not drawn to a surfactant forming a monolayer. And even it they were, Unger et al clearly define their vesicles as spherical entities

formulated from lipids in the form of a monolayer or a bilayer, wherein examples of vesicles are micelles and liposomes (column 7, lines 49-51, column 17, lines 50-53, column 27, lines 35-40). Therefore, it is clear from their disclosure that Unger et al. define the vesicles as a genus that includes a variety of species, among which are monolayer and bilayer vesicles. Since Unger et al. redefined the term "vesicles", one of skill in the art would have readily recognized that the genus of vesicles would necessarily include monolayer micelles.

Claim Rejections - 35 USC § 103

5. Claims 66, 67, 87-94, 101, 133, and 134 are rejected under 35 U.S.C. 103(a) as being unpatentable over Unger EC et al., as applied to claims 66, 67, 87, 88, 90-92, 94, and 101 above, in view of Schneider et al. (FEBS Letters, 1998, 429: 269-273) for the reasons of record set forth in the prior Office action. Applicant's arguments filed on 01/05/2007 have been fully considered but they are not persuasive.

Applicant traversed the instant rejection on the grounds that Schneider et al. do not remedy the deficiencies of Unger et al. Applicant argues that the methods of Unger et al. specifically for producing particles comprising proteins result in protein particles having a minimum size of 200 nm in diameter (Example 39A), and therefore, even if one of skill in the art would be able to use the method of Unger et al. to prepare tenascin particles, these particles would necessarily have a diameter of about 200 nm and such particles would be outside the scope of the claims. Applicant also argues that there is no reasonable expectation of success from the suggestion of Scheider et al. that

tenascin would act as a targeting ligand because tenascin must be in the correct three-dimensional structure and present its active site on the exterior of the particle. Applicant argues that, since it is known in the art that proteins are subject to misfolding, aggregation, and denaturation in expression systems and/or upon purification or manipulation, the success with tenascin as the targeting moiety is not assured. Applicant argues that she, unexpectedly, found success by using tenascin as a targeting moiety. With respect to the critical micelle concentration (CMC) (claim 89), Applicant submits that Example 1 of the instant specification shows a series of non-working compositions, wherein all detergents with a CMC greater than 200 micromolar failed to generate functional particles. Therefore, this is not a mere optimization that Applicant carried out, but rather an inventive discovery. Applicant submits that the instant particles have unexpectedly superior qualities as compared to liposomes, dendrimers, or standard polyplexes of DNA and PEI (Examples 2 and 3) because they are taken up by caveolae and thus avoid lysosomes within a cells (which are known to be an impediment to successful gene therapy) and this is an inventive finding. Therefore, Applicant requests the withdrawal of the rejection. Additionally, Applicant submits that claim 93 is listed as rejected for obviousness and it is not rejected as anticipated by Unger et al. Moreover, it is not argued by the Examiner that Schneider et al. teach the limitations of the claim. Therefore, Applicant asserts that claim 93 is free of prior art and requests the indication of the allowability of the claim.

Applicant's arguments are acknowledged, however, the rejection is maintained for the following reasons:

While it is true that Unger et al. teach protein particles, wherein the particles contain a bioactive component core and the protein in association with the bioactive agent, this is just one embodiment of the particles taught by Unger et al. It is noted that the rejection is not based on this particular embodiment. As stated above and in the prior Office action, the instant rejection is based on the disclosure in Unger et al. of particles comprising a core made of bioactive components and a surfactant such as cetyl alcohol in association with the bioactive components. Unger et al. teach that their particles are coated with a biocompatible polymer that provides a targeting ligand for specific cellular uptake, wherein the biocompatible polymer can be a protein or a polypeptide (see above and the prior Office action and also column 13, lines 49-59). However, Unger et al. do not specifically teach tenascin. Since Schneider et al. teach that polypeptides derived from the C-terminus of tenascin are capable to mediate specific gene delivery to cells expression receptors for tenascin, such as airway epithelial cells, one of skill in the art would have known and would have been motivated to modify the particles of Unger et al. by using the polypeptides of Schneider et al., or in alternative, the full length tenascin to coat (i.e., the active sites are presented on the exterior of the particles). Since cetyl alcohol is used to make the particles, these particles must have a diameter of about 50 nm (see above). Therefore, Applicant's argument that combining the teachings of Unger et al. and Schneider et al. would result in particles with a diameter of about 200 nm is not found persuasive. Furthermore, Applicant argues that, since it is known in the art that proteins are subject to misfolding in expression systems or upon manipulation, the success in using tenascin as a

targeting ligand is not assured. First, it is noted that an obviousness-type rejection does not require an assurance of success; it requires only a reasonable expectation of success. Second, this again is an argument not supported by any evidence. The art teaches that proteins can be used to coat particles and target the particles to specific cell targets (see for example Unger et al.) and there is no evidence in the art that tenascin would not behave in a similar manner. The level of one of skill in the art is such that he/she would readily realize the importance of maintaining and using the proper conditions to preserve the three-dimensional structure of tenascin. Applicant did not provide any evidence that obtaining tenascin in the correct conformation requires more than routine experimentation. With respect to the argument that finding the right CMC is an inventive discovery, it is noted, although it requires work, testing different surfactants for their capacity to render particles of desired size and activity is routine experimentation. With respect to the argument that the instant particles have unexpected superior qualities as compared to other types of particles, it is noted that the particles of Unger et al. must have the same qualities (i.e., be taken up by caveolae) because they have the same size. With respect to the argument that claim 93 is free of prior art, it is noted that claim 93 was included in the obviousness-type rejection and therefore, it is not free o f prior art. Claims 93 was not argued because the limitations disclosed in claim 93 are not innovative over the prior art. Claim 93 broadly recites "a water-miscible solvent or a combination of water-miscible solvents". Therefore, any solvent (even water) used to dissolve the bioactive component that forms the core of the particle, as long as it is water-miscible, can be considered to meet the limitations of the

claim. Therefore, the claimed invention was *prima facie* obvious at the time the invention was made.

New Rejections

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 66, 67, 87, 88, 90-92, 94, 101, 135, and 136 are rejected under 35 U.S.C. 103(a) as being unpatentable over Unger et al., in view of both Medina (U.S. Patent No. 5,650,543) and Quay (U.S. patent No. 5,707,606).

The teachings of Unger et al. are applied as set forth above and in the prior Office action for claims 66, 67, 87, 88, 90-92, 94, 101, and 135. Unger et al. do not teach acetylenic diols (claim 136). Medina teaches ethoxylated acetylenic diols as excellent surfactants because of their ability to decrease the surface tension (Abstract, column 1, lines 30-35, column 3, lines 3-5). Medina does not teach using their surfactant for the fabrication of nanoparticles. However, Quay teaches the use of acetylenic diols or blends thereof for the preparation of stable and biocompatible colloidal dispersions used for enhancing the contrast in an ultrasound image (Summary of the invention, column 7, lines 9-16). Based on the teachings of Quay one of skill in the art would have known that acetylenic diols could be used to obtain biocompatible

particles suitable for the delivery of bioactive agents. Based on the teachings of Medina (i.e., the ability to decrease the surface tension), one of skill in the art would have known that the use of acetylenic diols would result in small particles that are more efficient in delivering bioactive components. Therefore, it would have been obvious to one of skill in the art, at the time the invention was made, to modify the particles of Unger et al. by using acetylated diols, with a reasonable expectation of success. One of skill in the art would have been motivated to do so because Medina clearly teaches that such surfactants are able to decrease the surface tension. One of skill in the art would have been expected to have a reasonable expectation of success in making such a composition because the art teaches that acetylenc diols can be successfully used in the preparation of particles for the *in vivo* delivery of agents. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Conclusion

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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